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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,200	03/22/2006	Se Hwan Yang	58049-00025	4449

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EXAMINER	
WANG, CHANG YU	
ART UNIT	PAPER NUMBER
1649	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,200	YANG ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/27/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,10,11,13 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,10,11,13 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/22/06* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendment filed 10/27/08 is acknowledged. Claims 2-7, 9, 12, and 14-16 are cancelled. Claims 1, 10, 11, and 13 are amended. Claim 17 is newly added. Claims 1, 8, 10, 11, 13 and newly added claim 17 are pending in this application and under examination in this office action.

2. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

3. Applicant's arguments filed on 10/27/08 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Drawings

4. The drawings/figures stand objected to because sequence listings included in the specification must not be duplicated in the drawings. See 37 C.F.R. §1.58(a) and §1.83. On p. 5 of the response, Applicant states that at which time Applicant will make the necessary revisions to the drawings/figures. The objection is maintained of record until the correction is made.

Claim Rejections/Objections Withdrawn

5. The objection to claims 1, 12, 14 and 15 is withdrawn in response to Applicant's amendment to the claims and cancellation of claims 14 and 15.

The rejection of claims 7, 10 and 16 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in response to Applicant's amendment to the claims and cancellation of claims 7 and 16.

The rejection of claims 1-16 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in response to Applicant's amendment to the claims and cancellation of claims 2-7,9, 12 and 14-16.

The rejection of claim 7 under 35 U.S.C. 112, second paragraph, as being indefinite is moot because the claim is canceled.

The rejection of claims 1, 5, 8-9, and 11-15 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,674,711 as evidenced by US 6,632,637 is withdrawn in response to Applicant's amendment to the claims and cancellation of claims 5, 9, 12 and 14-15.

The rejection of claims 1-3, 5-6, 8-9 and 11-15 under 35 U.S.C. 103(a) as being unpatentable over US 5,674,711 in view of US2003144189, US 6,632,637, US 6,136,536, US20030083242, and US 6,852,510 is withdrawn in response to Applicant's amendment to the claims and cancellation of claims 2-3, 5-6, 9, 12 and 14-16.

Claim Rejections/Objections Maintained

In view of the amendment filed on 10/27/08, the following rejections are maintained.

Claim Objections

6. Claim 17 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 17 recites the limitation that has been already recited in instant claim 1, which does not further limit claim 1.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 8, 11, 13 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,674,711 in view of US2003144189, US 6,632,637, US 6,136,536, US20030083242, US 6,852,510 and further in view of Logan et al. (Proc.

Natl. Acad. Sci. USA, 1984, 81:3655-3659) and WO03/048366. The rejection is maintained for the reasons made of record.

Claims 1, 8, 11, 13 and 17 as amended are drawn to an expression vector, a transformant and a method of making human FSH protein wherein the expression vector comprises 1) a gene encoding human FSH consisting of human FSH beta subunit gene having the sequence of SEQ ID NO2, internal ribosomal entry site (IRES) sequence having the sequence of SEQ ID NO:7, and alpha human FSH subunit gene having the sequence of SEQ ID NO:1, 2) a promoter sequence of early gene of CMV having the sequence of SEQ ID NO:8, 3) a tripartite leader sequence of adenovirus having the sequence of SEQ ID NO:9, 4) a polyadenylation motif sequence of early gene of SV40 virus having the sequence of SEQ ID NO:13 and/or a polyadenylation motif sequence of bovine growth hormone (BGH) gene having the sequence of SEQ ID NO:14 and 5) a dihydrofolate reductase (DHFR) gene having the sequence of SEQ ID NO:12 wherein the vector expresses FSH beta and alpha subunits that form a glycosylated FSH heterodimer.

On p. 9 of the response, Applicant argues that none of the cited references teach or suggest an expression vector simultaneously encoding individual subunit polypeptides of a heterodimeric protein, separated by an IRES sequence. Applicant argues that a skilled artisan would not predictably arrive at the instant invention. Applicant also argues that although yeast and insect cell-based expression systems can produce glycosylated proteins, they did not produce a sufficient amount of active FSH as glycosylated heterodimeric FSH produced in transfected CHO cells. Applicant argues

that it is only hindsight to arrive at the instant invention. Applicant's arguments have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this case, US 5,674,711 (the '711 patent) teaches a recombinant transformant for producing human FSH comprising an expression vector (CLH3AXSV2) comprising a gene encoding human FSH alpha or beta, a promoter sequence (a mouse metallothionein-I (MT-1) promoter), a polyadenylation (polyA) motif sequence (a SV40 early polyA motif) and a dihydrofolate reductase (DHFR) gene (a mouse DHFR gene)) (see cols. 3-13; figure 4; examples 1-6, in particular). Although the '711 patent does not explicitly teaches SEQ ID NOs:1 & 2 encoding human FSH alpha and beta subunits respectively, US2003144189 teaches the amino acid sequences of human FSH alpha and beta subunits. US2003144189 teaches a DNA sequence having 99.5% identity to instant SEQ ID NO:1 to encode human FSH alpha subunit and a DNA sequence having 98.8% identity to instant SEQ ID NO:2 to encode human FSH alpha subunit. The translated amino acid sequence human of US2003144189 is identical to the amino acid sequence encoded by instant SEQ ID NO:1. Although there is one-amino acid mismatch (cysteine vs valine) in the human FSH beta subunit of US2003144189, the FSH of the instant application is expected to have the same activity as that of

US2003144189 because cysteine and valine residues are conserved amino acids and thus would not change the activity of FSH.

Although the '711 patent does not explicitly teach SEQ ID NO:13 as a polyA motif sequence, the sequence of a polyA motif in the early gene of SV40 virus is known in the art as evidenced by US 6,632,637. In addition, the '711 patent teaches that FSH functions as a dimer containing FSH alpha and beta subunits (see col.1, lines 33-65, in particular). The '711 patent also teaches co-expression human FSH alpha and beta subunits by co-transfecting an expression vector containing a FSH alpha subunit gene and an expression vector containing a FSH beta subunit gene in CHO/DHFR- cells (see cols. 2-4, examples 1-2; col.14-16, claims 1-16, in particular). The '711 patent teaches a method of making human FSH protein (related to clams 11 and 13) (see col.4, line 32-col.6, line 21; examples 1-6, in particular).

Although the '711 patent does not teach an IRES sequence in an expression vector, US Patent No. 6,632,637 (the '637 patent) teaches an expression vector that can express at least two exogenous genes wherein the two exogenous genes are separated by an internal ribosomal entry site (col.1, line 38-col.2, line 63). The '637 patent teaches a method of making protein (related to claims 11 and 13) and a transformant of DHFR- CHO cell line (related to claim 8) containing an expression vector (related claim 1) containing an a CMV promoter, an IL4R gene, an IRES, a DHFR gene and a SV40 polyA sequence (instant SEQ ID NO:13) and a polyA sequence of BGH (instant SEQ ID NO:14) (see figure 1; col.2, line 13-col.6. line 35; col.6 table1; col. 29-32, claims 1-44; col.7, line 1-col.9, line 55, in particular).

Although the '637 patent does not explicitly teach instant SEQ ID NO:7 as a DNA sequence for IRES, US patent No. 6,852,510 (the '510 patent) teaches a DNA sequence of IRES having a DNA sequence 97% identical to instant SEQ ID NO:7. The N-terminus of the IRES DNA sequence of the '510 patent is different from that of the instant SEQ ID NO:7 with a 10-nucleotide mismatch. These 10 nucleotides are for different restriction enzyme sites and are not essential for ribosomal entry because both IRES DNA sequences have the same function for internal ribosomal entry. Although the '637 and '510 patent do not explicitly teach the DNA sequence for a CMV promoter, US20030083242 teaches a CMV promoter having a DNA sequence 99.3% identical to instant SEQ ID NO:8. The 3-nucleotide mismatch to instant SEQ ID NO:8 at the C-terminus as disclosed by US20030083242 is not essential because both of the CMV sequence have the same function to serve as a promoter.

Although the '711 patent does not explicitly teach SEQ ID NO:12 as a sequence for a DHFR gene as recited in instant claims, US 6,136,536 teaches the DNA sequence of DHFR (instant SEQ ID NO:12). Although the '711 patent does not teach SEQ ID NO:9 for a tripartite leader sequence of adenovirus, WO03/048366 teaches that an adenovirus tripartite leader sequence having 100% identity to instant SEQ ID NO:9 and Logan et al. teach that an adenovirus tripartite leader sequence can enhance translation of mRNA (see p. 3655, abstract; p. 3656, 2nd col., 4th paragraph, in particular).

It would also have been obvious to one of ordinary skill in the art at the time the instant invention was made to combine the teachings of US5,674,711, US2003144189, US6,632,637, US 6,136,536, US20030083242, US6,852,510, Logan et al. (Proc. Natl.

Acad. Sci. USA, 1984, 81:3655-3659) and WO03/048366 to generate an expression vector to express a glycosylated FSH heterodimer. The skilled artisan would have been motivated to do so with an expectation of success because the '711 patent teaches a functional FSH requires both of alpha and a beta FSH subunits, and the '637 patents teach a method of making proteins using a transformant of DHFR- CHO cell line containing an expression vector that contains a CMV promoter, an IRES, a DHFR gene and a SV40 polyA sequence and a polyA sequence of BGH to express two different proteins simultaneously. In addition, the claimed invention is obvious over the applied references and is expected to generate a glycosylated FSH heterodimer because US2003144189 teaches the DNA sequences of SEQ ID NOs: 1 and 2 for human FSH alpha and beta subunits, the '510 patent teaches the DNA sequence of SEQ ID NO:7 for IRES, US20030083242 teaches the DNA sequence of SEQ ID NO:8 for a CMV promoter, the '637 patent teaches the DNA sequences of SEQ ID NO:13 and 14 for SV40 and BGH poly-A motifs, the '536 patent teaches the DNA sequence of SEQ ID NO: 12 for DHFR, WO03/048366 teaches the DNA sequence of SEQ ID NO:9 for an adenovirus tripartite leader sequence and Logan teaches that an adenovirus tripartite leader sequence can enhance translation of mRNA.

Note that

The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)". See MPEP § 2144.07.

In this case, the instant claims are obvious over the cited references because all the claimed elements were known in the prior art and one skilled in the art could have

arrived at the claimed invention by using known methods to yield predictable results or to use these known technique to improve similar products in the same way.

On p. 9 of the response, Applicant argues that it is only hindsight to arrive at the instant invention. Applicant's arguments have been fully considered but they are not persuasive.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In addition, in considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to drawn therefrom. *In re Preda*, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968).

Conclusion

Allowable Subject Matter

8. Claim 10 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. NO CLAIM IS ALLOWED.

10. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
January 26, 2009

/Christine J Saoud/
Primary Examiner, Art Unit 1647